

REGULAR ARTICLE

Manipulation of oral medication for children by parents and nurses occurs frequently and is often not supported by instructions

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ABSTRACT

Aim: Due to a lack of age-appropriate formulations, administration of drugs to children remains a challenge. This study aimed to identify the problems experienced in both the outpatient setting and the clinical setting.

Methods: Between June 2017 and January 2018, we performed a cross-sectional, prospective study at the Sophia Children's Hospital, The Netherlands. The study comprised of a structured interview on drug manipulations with parents visiting the outpatient clinic, and an observational study of drug manipulations by nurses at the wards.

Results: A total of 201 questionnaires were collected, accounting for 571 drugs and 169 manipulations (30%). Drug substances that were most often mentioned as manipulated were macrogol ($n = 23$), esomeprazole ($n = 15$), paracetamol ($n = 8$), methylphenidate ($n = 7$) and melatonin ($n = 7$). Of all manipulated medicines, 93/169 (55%) were manipulated according to the instructions or recommendations of the Summary of Product Characteristics (SmPC) or patient information leaflet. During the observational study, manipulation was performed by 21/35 of observed nurses (60%), of whom 11 deviated from the hospital protocol for manipulation or SmPC (52%).

Conclusion: Manipulation was a widely used method to administer drugs to children. Validated information regarding manipulation of drugs for both parents and nursing staff is needed.

INTRODUCTION

The administration of medicines to paediatric patients remains a challenge for both parents and healthcare professionals. The lack of age-appropriate pharmaceutical preparations for children, primarily with respect to accuracy of dosage and routes of administration, contributes mainly to this barrier (1,2).

Van Riet-Nales et al. showed that in 2009 only 48% of available medicines for human use were authorised for one or more paediatric age groups (1), and the 10-year report by the European Commission on the Paediatric Regulation confirms the lack of progress for off-patent medicines (3). Furthermore, a paediatric indication in the label does not necessarily mean that the dosage form is suitable for use in children (1). The inventory of needs for paediatric medicines from the European Medicines Agency (EMA) still shows there is a lack of age-appropriate paediatric medicines in a considerable number of therapeutic areas (4). This lack of age-appropriate medicines forces parents and

caregivers to apply manipulation techniques to the medicine in order to achieve the appropriate dose or to make the medicine acceptable to their children (2). In the clinical setting, manipulation also occurs frequently, either within the pharmacy in the preparation of extemporaneous medicines or in the wards at the moment of administration (5).

There are risks attached to the manipulation of medicines. Richey et al. (6) summarised the evidence for the use of dosage form manipulation to obtain the required dose. Multiple researchers showed that splitting tablets by hand,

Abbreviations

MODRIC, Manipulation Of Drugs In Children; PIL, Patient information leaflet; SmPC, Summary of product characteristics.

Key notes

- Due to a lack of age-appropriate formulations, drug administration to children remains a challenge.
- This study aimed to identify the methods and reasons used for manipulation of medicines to aid administration, in both the inpatient and outpatient setting.
- Manipulation was a widely used method, often unsupported by validated instructions, demonstrating the need for age-appropriate medicines that can deliver correct dosages.

with a kitchen knife or even a tablet splitter caused inconsistent results in terms of dose accuracy (7–12). Dispersing tablets in water and taking a portion of the obtained suspension is another method to adjust the dose. However, doses may vary depending on where the samples are taken from the container used to disperse the drug, especially for poorly water-soluble drugs (13). Moreover, drug loss during manipulation can be a significant problem, depending on the medicine, operator and method used (6).

Besides the possible negative effects on dose accuracy, accompanying risks of manipulation include possible negative effects on stability, solubility and bioavailability, with subtherapeutic or even toxic drug levels as an unwanted result (14,15). For certain medicines, there is also a risk for the parent or caregiver when they are exposed to the drug substance. Lastly, manipulations are time-consuming and could increase the risk of errors, given the fact that drug calculation errors are the most common type of errors in neonatal and paediatric practice (2). Therefore, there is a need to standardise procedures to reduce the risks associated with manipulation. In the Netherlands, a reference work for manipulation of drugs, *Oralia VTGM*, is issued by *The Royal Dutch Pharmacists Association*, and available via subscription (16).

In summary, various studies showed the risks of drug manipulation, induced by the lack of authorised and age-appropriate paediatric medicines, but few studies have evaluated the extent and type of manipulation. The aim of this study was to identify the problems in the administration of medicines to children experienced by both parents and caregivers in the outpatient setting, as well as by nurses in the clinical setting, by determining the extent, reasons and methods used for drug manipulation.

A secondary objective was to identify the information sources used to execute manipulation, in order to identify gaps in the availability of instructions.

METHODS

Study design

We performed a cross-sectional, prospective study at the Erasmus MC-Sophia Children's Hospital, a tertiary referral hospital in Rotterdam, The Netherlands, between July 2017 and January 2018. The study consisted of two parts. First, we conducted a survey on drug manipulations by parents and caregivers of outpatients, in order to determine the methods and tools used. Second, we conducted a structured, undisguised, observational study of drug manipulations by nurses at the paediatric wards. These observations of the administration of medicines to paediatric patients by nurses have been used to determine the frequency and types of manipulations. For the purpose of this study, manipulation was defined as 'the physical alteration of a pharmaceutical drug dosage form for the purpose of extracting and administering the required proportion of the drug dose'. This definition is based on the Manipulation Of Drugs In Children (MODRIC) guidelines from the Alder Hey Children's Hospital (17).

In addition, medicines co-administered with food or liquids that are not explicitly recommended, without physical alteration of the dosage form, were also accounted as manipulation.

Manipulations by parents and caregivers in the outpatient setting

Questionnaire

An electronic questionnaire was built using the web-based LimeSurvey version 2.06 (LimeSurvey GmbH, Hamburg, Germany). The questions were derived from sources regarding the manipulation of medicines for paediatric administration, such as the MODRIC guidelines, and additional research regarding manipulation of medication in children (2,6,18–21). Questions gave insight into the extent, reasons and methods of manipulation of oral dosage forms for children by parents and caregivers, and included six topics: demographic data, current medication, methods and reasons for manipulation, medication adherence in relation to manipulation, the possible combined administration of oral medicines and the sources of information consulted regarding manipulation. An English translation of the questionnaire is available in Appendix S1. Before start of data collection, the questionnaire was reviewed by pharmacy technicians from the outpatient pharmacy of the Erasmus MC, to test the length of the questionnaire and the comprehensibility of the questions for parents and children. After processing the feedback from the pharmacy technicians, the questionnaire was piloted using 20 participants of the target group, to resolve any remaining ambiguities in the questions. The results from this pilot were not included in the analysis.

Recruitment

Participants were recruited at the outpatient clinics representing all major paediatric subspecialties, and before and after the medication reconciliation visits related to hospital admission. Inclusion criteria were the use of oral medication and age below 18 years. Insufficient command of the Dutch language was an exclusion criterion. The questionnaire was filled in by the researcher whilst interviewing the parent or caregiver and patient. With permission from the participants, we verified and supplemented the answers regarding current medication with their outpatient medication list retrieved from the outpatient pharmacy or their local pharmacy, to confirm which specific medicine and brand was used.

Manipulations by nurses at the inpatient wards

To assess the extent and ways of drug manipulation by nurses, the researcher observed the administration of oral medication to paediatric patients. Nurses were informed of the intention of the study: to improve drug therapy in patients, and not to assess any individual performances. Observation of paediatric nurses took place for one week in each of the six wards: paediatric intensive care unit, neonatal intensive care unit, oncology, neurology/neurosurgery, general paediatrics and paediatric surgery/

paediatric thorax centre. A minimum of five nurses were observed at each ward.

Data analysis

After collection of the data, the manipulations were compared to the patient information leaflet (PIL), or the summary of product characteristic (SmPC) or the local hospital protocol for drug manipulation and administration, to check if they were performed according to any of the instructions.

Age categories were defined according to the guideline on clinical investigation of medicinal products in the paediatric population (22), and all patients admitted to the NICU were categorised as preterm neonates.

Ethical approval

The Erasmus MC Medical Ethics Committee reviewed the research proposals of both study parts and decided that they did not fall within the scope of the Medical Research Involving Human Subjects Act (ref no. 2017–276 and 2017–1092). Nevertheless, participants in the questionnaire were asked for written consent.

RESULTS

Manipulations by parents and caregivers in the outpatient setting

Between June 2017 and January 2018, a total of 201 questionnaires were collected from parents and caregivers visiting the outpatient clinics of the Sophia Children's Hospital. The total number of oral medicines reported was 571. Patient characteristics are displayed in Table 1. Medication verification was consented to by 184/201 (92%) of the participants.

Methods and reasons for manipulation

The survey revealed that 105/201 (52%) respondents applied manipulation to one or more medicines before administration. Similar percentages for each age group were

found, ranging from 48% in infants and toddlers to 59% in school children. In total, 169/571 (30%) medicines were manipulated. Drug products that were most often mentioned as manipulated were macrogol powder and sachets, esomeprazole in several dosage forms, paracetamol tablets and syrup, methylphenidate tablets and melatonin tablets. We found no direct correlation between specific drugs products and type of manipulation, but manipulation because of dose adjustment was performed more often on tablets. Figure 1 displays the reasons for manipulation, divided per age group, with taste mentioned as main reasons for manipulation, followed by dose adjustment. Figure 2 displays the methods for manipulation, with mixing with a liquid mentioned most frequently, followed by breaking or splitting of a tablet.

Of all manipulated medicines, 93/169 (55%) were manipulated according to the instructions or recommendations of the SmPC or PIL and 69/169 (41%) were manipulated not fully according to the SmPC or PIL. For 7/169 manipulated medicines, which were extemporaneously compounded, no SmPC or PIL was available. Table 2 provides an overview of the types of manipulation, deviating from the SmPC or PIL.

Information sources

All respondents who replied to perform some form of manipulation by their own definition ($n = 116$) were asked if they had received information on manipulation, or acquired it themselves from any source. As displayed in Table 3, 45% of the respondents reported to have received explicit information on manipulation, and 13% of the respondents indicated to not have received any information when it might have been applicable. Verbal information was more common than written information, and the pharmacy was the most frequently cited source of information.

Manipulations by nurses at the inpatient wards

Observations of nurses at the wards took place during a study period of six weeks, and within this period, 115 drug administrations to 35 individual patients were observed, performed by 35 different nurses. Patient characteristics and qualification of the nurses are displayed in Table 4.

Methods and reasons for manipulation

Manipulation of the dosage form was required for 21/35 observed patients (60%). Also, manipulation was performed prior to 42/115 oral administrations (37%). Drug products that were most often manipulated were compounded spironolactone capsules, compounded hydrochlorothiazide liquid, esomeprazole granules and topiramate capsules and tablets. The frequencies of the performed methods for manipulation and the corresponding reasons are displayed in Figure 3. Drug manipulations prior to administration were compared to the instructions from the SmPC and the hospital protocol. Of the 42 observed manipulations, 26 (62%) were given conform SmPC or hospital protocol and 16 (38%) deviated.

Table 1 Patient characteristics ($n = 201$)

Age (years)	n	Median (IQR)	%
Term neonates (0–28 days)	0		0%
Infants and toddlers (1–23 months)	25	0.8 (0.3–1.5)	12%
Children, pre-school (2–5 years)	72	3.8 (3.0–4.6)	36%
Children, school (6–11 years)	63	8.0 (7.0–11.0)	31%
Adolescent (12–17 years)	41	14.0 (12.7–15.5)	20%
Total	201	6.0 (3.3–11.0)	100%
Sex			
Male	113		56%
Female	88		44%
Presence of feeding tube			
Nasogastric tube	10		5%
Percutaneous endoscopic gastrostomy	22		11%

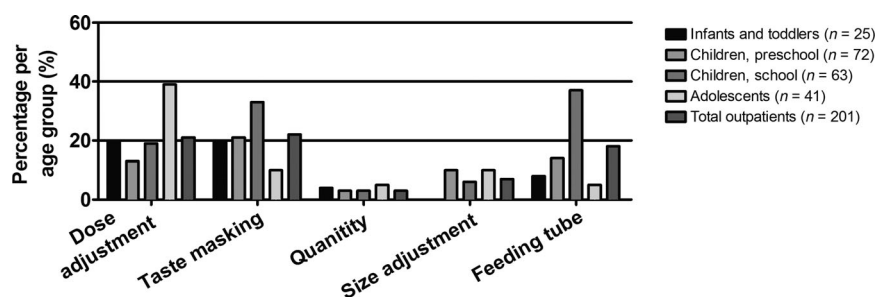


Figure 1 Percentage of parents or caregivers reporting a specific reason for manipulation of oral medicines (n = 201) per age group. Quantity: too many units (capsules or tablets) need to be administered to reach the correct dose.

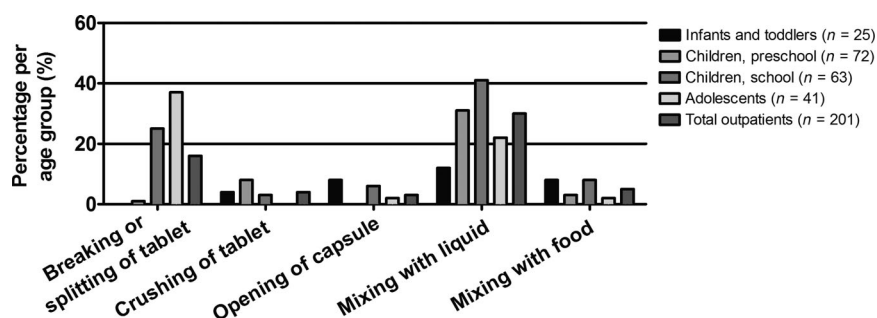


Figure 2 Percentage of parents or caregivers reporting a specific method for manipulation of oral medicines (n = 201) per age group.

Table 2 Classification of manipulation not according to the SmPC, with a definition of the type of manipulation

Type	Definition	Frequency	Percentage of total (n = 69)
Vehicle	Use of food or drink to aid administration other than what is recommended in the SmPC or PIL	36	52%
Dose	Manipulation that might not provide an accurate dose, such as splitting of unscored tablets	22	32%
Integrity	Affecting or breaking the integrity of a medicine by manipulation, such as crushing of coated tablets	8	12%
Mixing	Administration of multiple medicines by mixing them, for instance by adding the content of a capsule to a syringe with a liquid drug	6	9%
Safety	Manipulations that cause a risk for the parent or caregiver, such as crushing of methotrexate	2	3%

PIL, Patient information leaflet; SmPC, Summary of product characteristics.

Table 3 Information source used by parents and caregivers for drug manipulation

Instructions provided for manipulation	Frequency	Percentage of total (n = 116)
Yes	90	78%
No	26	22%
Type of communication		
Verbal	46	40%
Both	33	28%
Written	11	9.5%
Source of information		
Doctor	44	38%
Pharmacist or pharmacy technician	35	30%
Nurse	28	24%
Patient Information Leaflet	20	17%
Other	1	<1%
Internet	0	0%

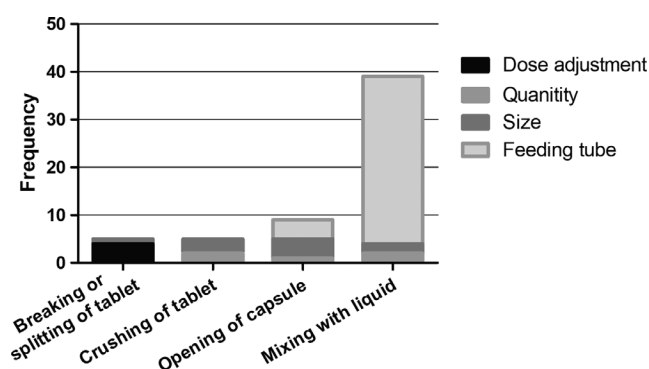
manipulation or SmPC (52%). Most often these deviations consisted of opening of capsules to mix the content with liquid, grinding of tablets with the risk of drug loss and mixing drugs with incompatible food or liquids, such as dairy. Nurses that performed manipulations were asked about any instructions that they received and information sources they consulted regarding the manipulation (Table 5).

Information sources

Manipulation was performed by 21/35 nurses (60%), of whom 11 deviated from the hospital protocol for

Table 4 Patient and nurse characteristics

Qualification nurses (n = 35)	Frequency	Percentage of total
Student nurse	2	6%
Registered nurse	8	23%
Advanced practice registered nurse	25	71%
Patient age category (n = 35)		
Preterm neonates (NICU)	4	11%
Term neonates (0–28 days)	2	6%
Infants and toddlers (1–23 months)	9	26%
Children, pre-school (2–5 years)	7	20%
Children, school (6–11 years)	5	14%
Adolescent (12–17 years)	8	23%
Sex (n)		
Male	21	60%
Female	14	40%
Use of feeding tube (n)	17	49%

**Figure 3** Observed methods of manipulation with corresponding reasons reported by nurses for 42 drug administrations. Quantity: too many units (capsules or tablets) need to be administered to reach the correct dose.

DISCUSSION

This study showed that manipulation of oral dosage forms is common practice among both parents and caregivers as well as nurses in a paediatric hospital, with a similar prevalence of 30% in the outpatient setting compared to 37% in the inpatient setting. Due to a broader definition of manipulation, including the co-administration with possibly incompatible food or liquids, the prevalence in our inpatient cohort was higher compared to the prevalence from a study in two Norwegian paediatric hospitals (37% versus 17%), but the prevalence in our outpatient cohort was equal to a cohort of outpatients from the UK using a similar definition (30% versus 29%) (23).

The predominant reasons for manipulation were different between the inpatient and outpatient setting. Manipulation by parents and caregivers in the outpatient setting occurred mainly to achieve a better taste and dose adjustment, whilst nurses in the inpatient setting most often used manipulation for administration through a feeding tube and size reduction. The inpatient and

Table 5 Information source consulted by nurses for drug manipulation

Instructions provided for manipulation	Frequency	Percentage of total (%)
Yes	16/21	76%
No	5/21	24%
Type of communication		
Verbal	9/16	56%
Written	6/16	38%
Both verbal and written	1/16	6%
Source of information		
Other nurses	10/21	48%
Oralia VTGM or hospital protocol	6/21	29%
Own knowledge/experience	4/21	19%
Doctor	1/21	5%

outpatient population are of course very different. The data showed a difference in age distribution, but also the nature and severity of the medical condition can be expected to be different. Nevertheless, we also consider the more extensive formulary of the inpatient pharmacy to be an important explanation, as it allows for more precise dosing with compounded liquids and low-dose capsules. The higher prevalence of feeding tubes in the inpatient setting explains why taste adjustment was not cited by the nurses as a reason for manipulation.

The predominant method of manipulation, both in the inpatient and outpatient setting, was mixing with liquids. In the inpatient setting, tube feeding and breast milk were commonly used matrices. When manipulation did not occur according to the instructions, this was most often because of co-administration with liquids or food not mentioned in the SmPC or PIL. Co-administration with liquids or food is often an acceptable strategy to administer drugs to children, but for certain drugs, food–drug interactions can have a significant effect on bioavailability and therapeutic effect (24). Even when such an interaction is known to the nurse, separated administration is not always possible due to administration of enteral feeding. Within our study, this was observed for both ciprofloxacin tablets and itraconazole liquid. Both the reasons and methods used for manipulation by parents and caregivers and nurses were similar to the Norwegian and UK studies, with taste being the most cited barrier to administration in the outpatient setting (18,23).

Many respondents to the questionnaire indicated to have received information on manipulation, but only half of them received this information from their pharmacy. This is an important finding, as guidance regarding the correct use of medication is one of the main tasks of the pharmacy, and pharmacists in the Netherlands have the Oralia VTGM reference book at their disposal. Similarly, only 29% of the nurses stated to have consulted the pharmacy-provided information regarding manipulation of the administered drugs, whilst 38% of the manipulations were not performed according to protocol. It demonstrates the need for additional in-service training of the nursing staff regarding drug

manipulation and the available reference works, available through the workstations in the hospital.

In the outpatient setting, taste was an important reason for manipulation, and administration with a vehicle not recommended was the most frequent manipulation not according to the SmPC or PIL. The macrogol containing laxatives were highly represented in this group, as they are very commonly prescribed and the SmPC or PIL recommends only water for administration. There is, however, no objection to mixing with other liquids from a biopharmaceutical standpoint. In the pharmacy of the Sophia Children's Hospital, the neutrally flavoured products are dispensed and parents are advised to use a fruit syrup to their child's liking to improve the taste. Ideally, the SmPC and PIL should give clear instructions on what food or drinks, if any, have been demonstrated to be appropriate for mixing with the paediatric preparation, as is now part of the Guideline on pharmaceutical development of medicines for paediatric use (22). Unfortunately, this information is not available for a lot of medicines, as the guideline applies only to newly developed medicines, and recommendations are made on the basis of physical-chemical formulation and drug characteristics. The absence of standard methods or criteria that define what flavours are acceptable to children, and the absence of common vehicles which are widely accepted and available, complicate the compatibility studies needed to form the recommendations regarding the intake with food and liquids (24,25).

Strengths and limitations

This study took place at a tertiary paediatric hospital, with all the major and minor paediatric subspecialties available, which allowed us to collect a large and diverse data set. Identification of the difficulties experienced when administering formulations to children is essential for directing future formulation development work. To our knowledge, this was the first study to directly compare the inpatient and outpatient setting with regard to manipulation of oral medicines. The major limitation of this study was the absence of a validated questionnaire and an established definition of manipulation, which limits the comparison of results to other studies. A risk of inaccurate reporting exists with the use of the questionnaire, but missing information regarding current medication was very often retrieved via the patient's local pharmacy or hospital record.

This study was not designed to assess the clinical impact of the reported manipulations. For many drugs, a correctly performed manipulation will not affect the therapeutic performance. However, with every manipulation, there is a risk of error, and complicated manipulations also rely on correct information transfer from the healthcare professional to the parent/caregiver.

CONCLUSION

This study showed that there remains a need for age-appropriate medicines. To reduce the need for

manipulation, continuous efforts should be made to develop age-appropriate formulations providing both dosing flexibility as well as acceptable taste. Furthermore, as co-administration with food or liquids remains the most practiced strategy for drug administration, more elaborate and explicit information within the SmPC and PIL regarding suitable vehicles is warranted. Manipulation to obtain the required dose occurred frequently, especially in the outpatient setting. Therefore, efforts should be made to reconcile the inpatient and outpatient formulary, to provide parents and caregivers with more dose-capable formulations. When a patient is discharged, there is an important task for the pharmacist/technician to properly inform parents and caregivers on manipulation and co-administration with food. Especially, when this information is not available in the PIL, and recommendations need to be generated based upon drug-specific characteristics, pharmacists are the eminent medicines experts. This also applies to community pharmacists that dispense possibly unsuitable drug products to paediatric patients.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1 Questionnaire.